

# The catecholamine biosynthetic pathway in DBH deficiency

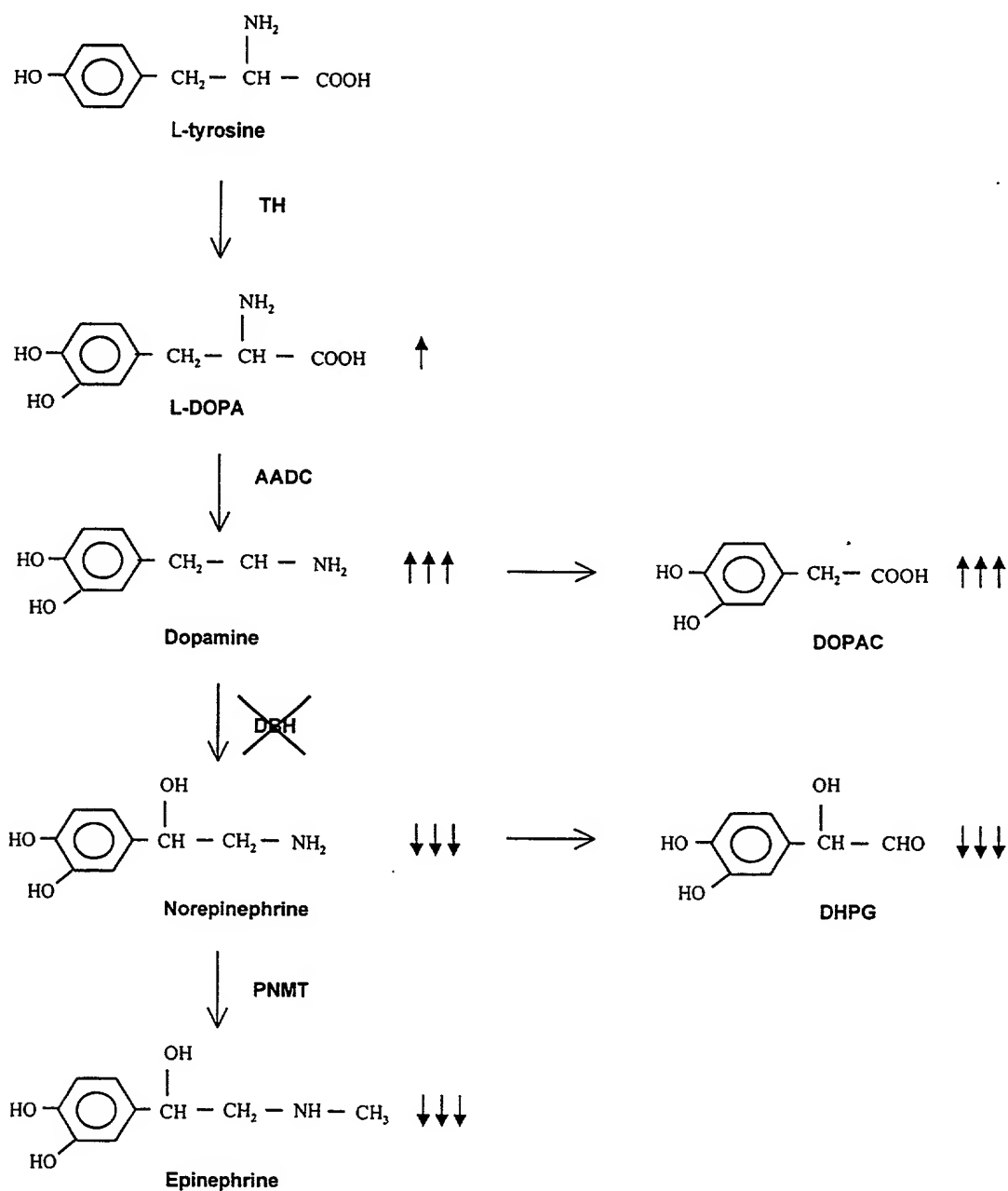
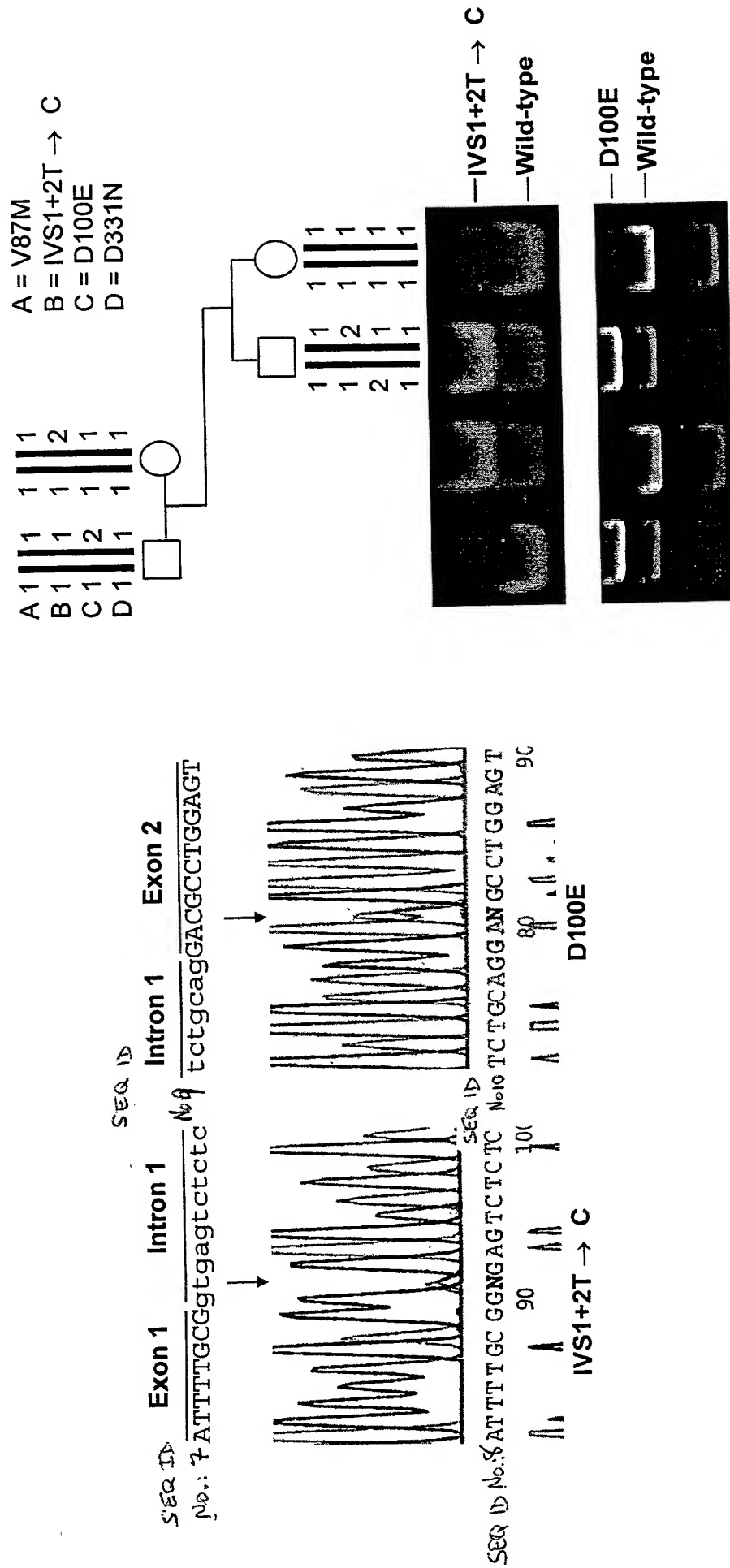


Figure 1

# Putative disease-causing mutations in DBH deficiency patient 1

Figure 2 B

Figure 2 A



# Putative disease-causing mutations in DBH deficiency patient 2

Figure 2 C

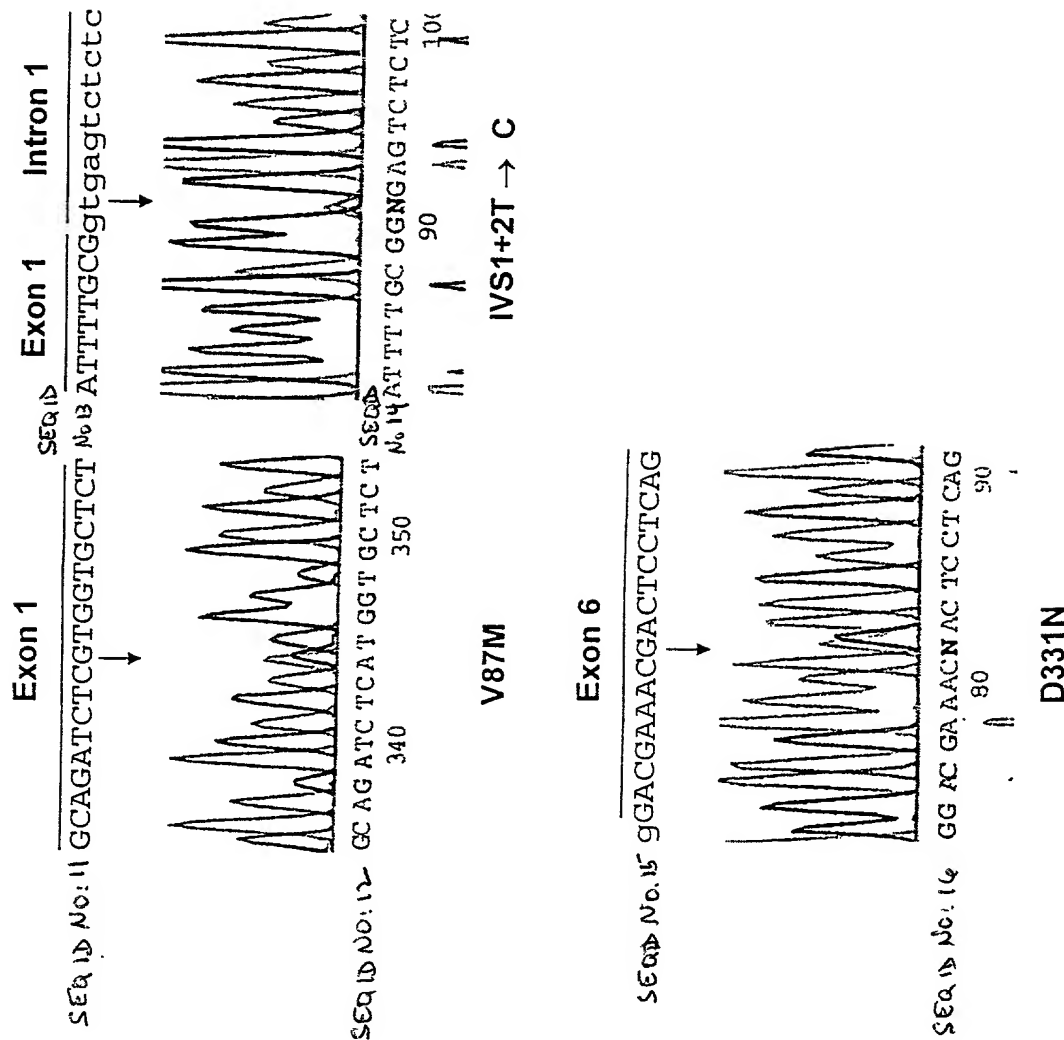


Figure 3 A

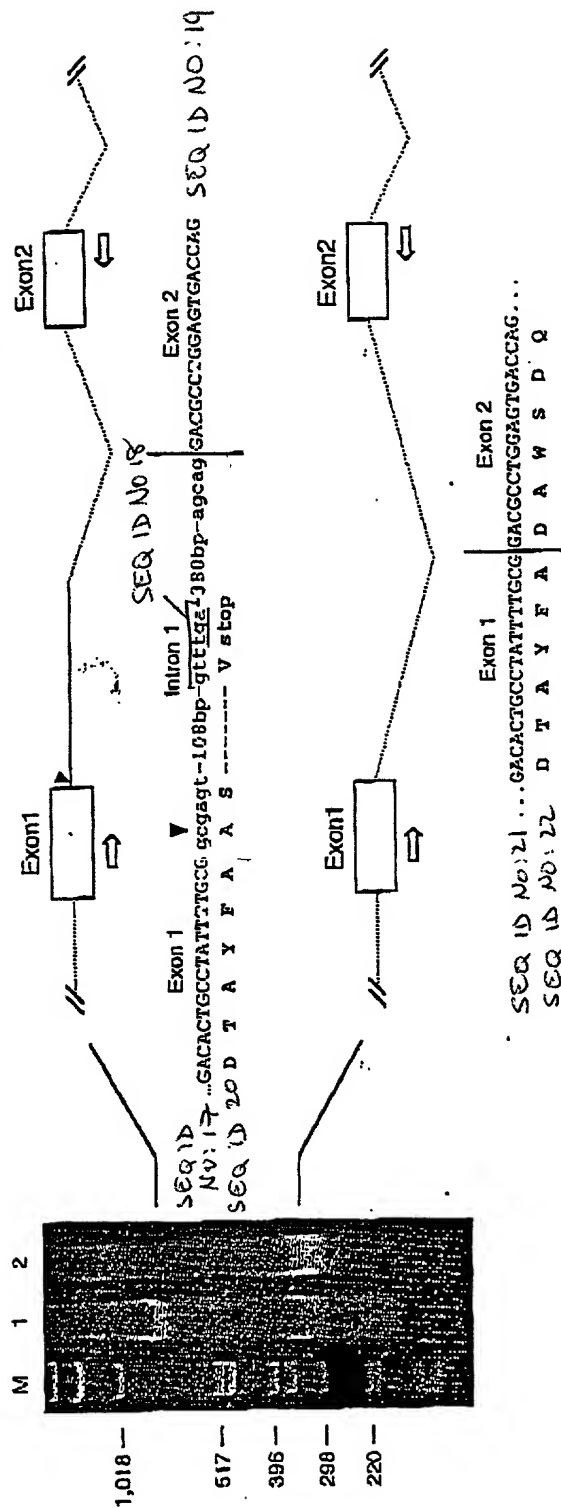


Figure 3 B

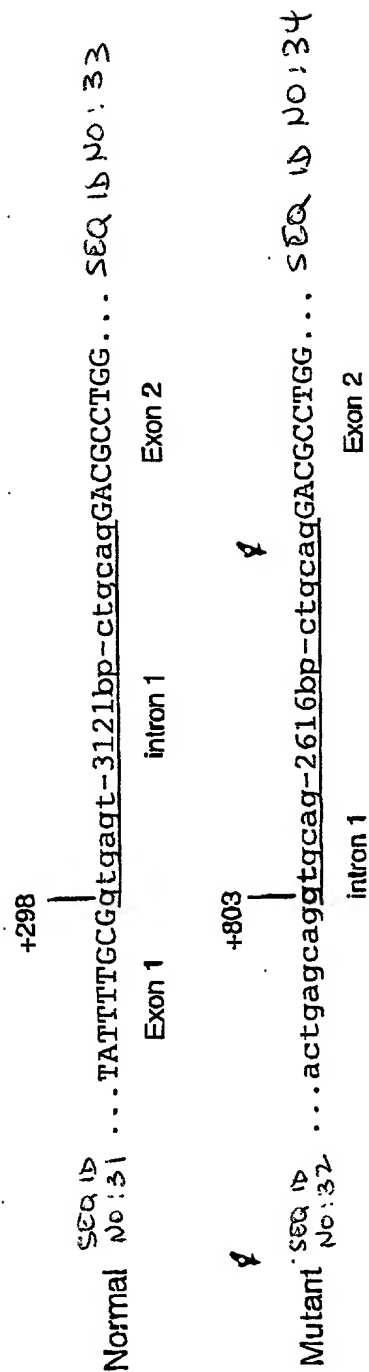


Figure 3

	87 <sup>th</sup>	100 <sup>th</sup>	
Mouse DBH	ENADI	LW-DGD-AYF...	ADAWSD-KGQ SEQ ID No 23
Rat DBH	ENADIV	LWTDGD--YF...	ADAWSDQKGQ SEQ ID No 24
Bovine DBH	ENADIV	VVLWTD-D-A-F...	ADAWSDQKGQ SEQ ID No 25
Human DBH	ENADIV	VVLMTDGDYTF...	ADAWSDQKGQ SEQ ID No 26
D.Melanogaster TBH	--AD--	-----F-----	

	331 <sup>th</sup>	
Mouse DBH	I-GR-DSSGIR	SEQ ID NO: 27
Rat DBH	I-GR-DSSGIR	SEQ ID NO: 28
Bovine DBH	I-GR-DSSGIR	SEQ ID NO: 29
Human DBH	IEGRDSSGIR	SEQ ID NO: 30
D.Melanogaster TBH	--G--D-SG-R	
Human PAM	-----D-SG--	

Figure 4

**Table 1. PLASMA LEVELS OF CATECHOLAMINES AND THEIR METABOLITES IN CONTROLS, PATIENTS WITH AUTONOMIC DISORDERS, AND DBH DEFICIENCY.**

	Dopa	DA	DOPAC	NE	DHPG	Epinephrine
Normal (n=15)	1,790 ± 150	20 ± 10	2,390 ± 480	252 ± 30	1,290 ± 110	28 ± 15
Pure Autonomic Failure (n=15)	1,300 ± 200	10 ± 10	1,030 ± 280	66 ± 26	627 ± 100	15 ± 8
Multiple System Atrophy (n=23)	1,780 ± 100	20 ± 12	2,300 ± 500	227 ± 27	1,340 ± 90	26 ± 16
DBH Deficiency Patient 1	2,723	172	15,200	<10	<10	<10
DBH Deficiency Patient 2	3,394	141	17,300	<10	<10	<10

In DBH deficiency, precursors of NE (dopa, dopamine) or metabolites (DOPAC) are raised, while products downstream of DBH (NE, epinephrine, DHPG) are absent or at extremely low levels. In contrast, only modest changes in catecholamines and their metabolites are observed in autonomic disorders, such as pure autonomic failure and multiple system atrophy, which do not directly involve impaired DBH. Units for all data are in pg/ml plasma.

**Figure 5**

**Table 2. SEQUENCE VARIANTS IDENTIFIED IN DBH DEFICIENT PATIENTS.**

Location	Variant <sup>a</sup>	Amino acid change	Minor allele frequency <sup>b</sup>
5' flanking	C-1021T	---	0.159
Exon 1	G259A	Val87Met	0
Intron 1	IVS1+2T→C	---	0.011
Exon 2	C300A	Asp100Glu	0
Intron 3	IVS3+8C→T	---	0.017
Exon 6	G991A	Asp331Asn	0
Intron 10	IVS10+415A→G	—	0.386

<sup>a</sup>Nucleotide positions are numbered according to the cDNA sequence for exons, or genomic sequence for the 5' flanking region, with the first nucleotide of ATG initiation codon as 1. Positions for introns are according to the genomic sequence starting from the G of the donor site invariant GT.

<sup>b</sup>N=88 unrelated European-Americans

TABLE 3

## Clinical features of six reported cases of DBH deficiency

Feature	Frequency (%)
Severe orthostatic hypotension > 40mm Hg	100
Impaired ejaculation*	100
Plasma dopamine >>> plasma norepinephrine	100
Sweating present	100
Sinus arrhythmia present	100
Pressor clonidine response	100
Pressor efficacy of DOPS	100
Ptosis	67
Complicated perinatal course	67
Nocturia	67
Hypoprolactinemia	67
High palate	50
Nasal stuffiness	50
Hypomagnesemia	33
Seizures (with hypotension)	33

\* Refers to male patients only (n=2).

Figure 7



# DBH Amino Acid Sequence

Met	Arg	Glu	Ala	Ala	Phe	Met	Tyr	Ser	Thr	Ala	Val	Ala	Ile	Phe	Leu
1				5					10					15	
Val	Ile	Leu	Val	Ala	Ala	Leu	Gln	Gly	Ser	Ala	Pro	Arg	Glu	Ser	Pro
			20					25					30		
Leu	Pro	Tyr	His	Ile	Pro	Leu	Asp	Pro	Glu	Gly	Ser	Leu	Glu	Leu	Ser
		35					40				45				
Trp	Asn	Val	Ser	Tyr	Thr	Gln	Glu	Ala	Ile	His	Phe	Gln	Leu	Leu	Val
	50					55				60					
Arg	Arg	Leu	Lys	Ala	Gly	Val	Leu	Phe	Gly	Met	Ser	Asp	Arg	Gly	Glu
65				70					75					80	
Leu	Glu	Asn	Ala	Asp	Leu	Val	Val	Leu	Trp	Thr	Asp	Gly	Asp	Thr	Ala
			85					90					95		
Tyr	Phe	Ala	Asp	Ala	Trp	Ser	Asp	Gln	Lys	Gly	Gln	Ile	His	Leu	Asp
		100						105					110		
Pro	Gln	Gln	Asp	Tyr	Gln	Leu	Leu	Gln	Val	Gln	Arg	Thr	Pro	Glu	Gly
		115					120					125			
Leu	Thr	Leu	Leu	Phe	Lys	Arg	Pro	Phe	Gly	Thr	Cys	Asp	Pro	Lys	Asp
	130					135					140				
Tyr	Leu	Ile	Glu	Asp	Gly	Thr	Val	His	Leu	Val	Tyr	Gly	Ile	Leu	Glu
145				150					155					160	
Glu	Pro	Phe	Arg	Ser	Leu	Glu	Ala	Ile	Asn	Gly	Ser	Gly	Leu	Gln	Met
			165					170					175		
Gly	Leu	Gln	Arg	Val	Gln	Leu	Leu	Lys	Pro	Asn	Ile	Pro	Glu	Pro	Glu
		180						185				190			
Leu	Pro	Ser	Asp	Ala	Cys	Thr	Met	Glu	Val	Gln	Ala	Pro	Asn	Ile	Gln
	195						200					205			
Ile	Pro	Ser	Gln	Glu	Thr	Thr	Tyr	Trp	Cys	Tyr	Ile	Lys	Glu	Leu	Pro
	210					215					220				
Lys	Gly	Phe	Ser	Arg	His	His	Ile	Ile	Lys	Tyr	Glu	Pro	Ile	Val	Thr
225				230					235					240	
Lys	Gly	Asn	Glu	Ala	Leu	Val	His	His	Met	Glu	Val	Phe	Gln	Cys	Ala
			245					250					255		
Pro	Glu	Met	Asp	Ser	Val	Pro	His	Phe	Ser	Gly	Pro	Cys	Asp	Ser	Lys
		260						265				270			
Met	Lys	Pro	Asp	Arg	Leu	Asn	Tyr	Cys	Arg	His	Val	Leu	Ala	Ala	Trp
	275						280					285			
Ala	Leu	Gly	Ala	Lys	Ala	Phe	Tyr	Tyr	Pro	Glu	Glu	Ala	Gly	Leu	Ala
	290					295				300					
Phe	Gly	Gly	Pro	Gly	Ser	Ser	Arg	Tyr	Leu	Arg	Leu	Glu	Val	His	Tyr
305				310					315					320	
His	Asn	Pro	Leu	Val	Ile	Glu	Gly	Arg	Asn	Asp	Ser	Ser	Gly	Ile	Arg
			325					330					335		
Leu	Tyr	Tyr	Thr	Ala	Lys	Leu	Arg	Arg	Phe	Asn	Ala	Gly	Ile	Met	Glu
	340						345					350			
Leu	Gly	Leu	Val	Tyr	Thr	Pro	Val	Met	Ala	Ile	Pro	Pro	Arg	Glu	Thr
	355						360					365			
Ala	Phe	Ile	Leu	Thr	Gly	Tyr	Cys	Thr	Asp	Lys	Cys	Thr	Gln	Leu	Ala
	370					375					380				
Leu	Pro	Pro	Ser	Gly	Ile	His	Ile	Phe	Ala	Ser	Gln	Leu	His	Thr	His
385				390					395					400	
Leu	Thr	Gly	Arg	Lys	Val	Val	Thr	Val	Leu	Val	Arg	Asp	Gly	Arg	Glu
			405					410					415		
Trp	Glu	Ile	Val	Asn	Gln	Asp	Asn	His	Tyr	Ser	Pro	His	Phe	Gln	Glu
			420					425					430		

Figure 8

Ile	Arg	Met	Leu	Lys	Lys	Val	Val	Ser	Val	His	Pro	Gly	Asp	Val	Leu
		435					440					445			
Ile	Thr	Ser	Cys	Thr	Tyr	Asn	Thr	Glu	Asp	Arg	Glu	Leu	Ala	Thr	Val
		450				455					460				
Gly	Gly	Phe	Gly	Ile	Leu	Glu	Glu	Met	Cys	Val	Asn	Tyr	Val	His	Tyr
465					470					475					480
Tyr	Pro	Gln	Thr	Gln	Leu	Glu	Leu	Cys	Lys	Ser	Ala	Val	Asp	Ala	Gly
			485						490					495	
Phe	Leu	Gln	Lys	Tyr	Phe	His	Leu	Ile	Asn	Arg	Phe	Asn	Asn	Glu	Asp
			500					505					510		
Val	Cys	Thr	Cys	Pro	Gln	Ala	Ser	Val	Ser	Gln	Gln	Phe	Thr	Ser	Val
		515					520					525			
Pro	Trp	Asn	Ser	Phe	Asn	Arg	Asp	Val	Leu	Lys	Ala	Leu	Tyr	Ser	Phe
	530					535					540				
Ala	Pro	Ile	Ser	Met	His	Cys	Asn	Lys	Ser	Ser	Ala	Val	Arg	Phe	Gln
545					550					555					560
Gly	Glu	Trp	Asn	Leu	Gln	Pro	Leu	Pro	Lys	Val	Ile	Ser	Thr	Leu	Glu
			565						570					575	
Glu	Pro	Thr	Pro	Gln	Cys	Pro	Thr	Ser	Gln	Gly	Arg	Ser	Pro	Ala	Gly
			580					585					590		
Pro	Thr	Val	Val	Ser	Ile	Gly	Gly	Gly	Lys	Gly					
		595					600								

Figure 8 (continued)

# DBH cDNA

```

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ggcaaaggct ga
1812

```

Figure 9

# DBH Genomic Sequence

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Figure 10





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cctagtttcc	agcagaggaa	gtgtggccca	gggaggttga	gtgtccaggg	tcacatagca	12360
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Figure 10 (continued)









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acacctccac	actgtaccga	atgccaaatg	caggtggtgt	gagcagggcg	cactaacctg	27000
cctaaaaata	aagcaccagg	ggaggggaag	gtaagaaacg	aaccagtctg	aagctgcgag	27060
ctgggttttt	cctccttata	tgagaccac	tgggtattcg	aggcatctaa	tttatcctgg	27120
gcccactggg	ctgtgggtcag	gaggccaggg	cctatgcaga	gttagtcgcg	taagggtgcc	27180

Figure 10 (continued)



**SEQ ID NO: Amino Acid at position 87**

38 ENADLXVLWTD  
39 DRGELENADLXVLWTDGDTAY  
40 LFGMSDRGELENADLXVLWTDGDTAYFADAW  
41 LKAGVLFGMSDRGELENADLXVLWTDGDTAYFADAWSDQKG

X indicates amino acid position 87. X may be valine, methionine, or a conservative substitution for either valine or methionine. X may also be absent.

**SEQ ID NO: Amino acid position 100**

42 DTAYFAXAWSQ  
43 WTDGDTAYFAXAWSQKGQIH  
44 DLVVLWTDGDTAYFAXAWSQKGQIHLDPQQ  
45 ELENADLVVLWTDGDTAYFAXAWSQKGQIHLDPQQDYQLL

X indicates amino acid position 100. X may be aspartic acid, glutamic acid, or a conservative substitution for those amino acids. X may also be absent.

**SEQ ID NO: Amino acid position 331**

46 IEGRNXSSGIR  
47 HNPLVIEGRNXSSGIRLYYTA  
48 LEVHYHNPLVIEGRNXSSGIRLYYTAKLRRF  
49 SRYLRLEVHYHNPLVIEGRNXSSGIRLYYTAKLRRFNAGIM

X indicates amino acid position 331. X may be aspartic acid, glutamic acid, or a conservative substitution for those amino acids. X may also be absent.

**Figure 11**